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(54) **METHODS, COMPOSITIONS AND SCREENS FOR THERAPEUTICS FOR THE TREATMENT OF SYNOVIAL SARCOMA**

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(58) **Field of Classification Search**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,056,883 B2 * 6/2006 Ito et al. 514/19.3
2011/0061116 A1 * 3/2011 Haldar et al. 800/10

OTHER PUBLICATIONS

Eilber et al. 2007; Chemotherapy is associated with improved survival in adult patients with primary extremity synovial sarcoma. *Annals of Surgery*. 246(1): 105113.*

Kadoch et al. 2013a; Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell* 153: 71-85.*

Kadoch et al. 2013b; Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nature Genetics*. 45(6): 592-602.*

Conger. 2013. Protein complex may play role in preventing many forms of cancer, study shows. At: med.stanford.edu/news/all-news/2013/05/protein-complex-may-play-role-in-preventing-many-forms-of-cancer-study-shows.html.*

Takenaka et al. 2010; Downregulation of SS18-SSX1 expression in synovial sarcoma by small interfering RNA enhances the focal adhesion pathway and inhibits anchorage-independent growth in vitro and tumor growth in vivo. *International Journal of Oncology*. 36: 823-831.*

Thaete et al. 1999; Functional domains of the SYT and SYT-SSX synovial sarcoma translocation proteins and co-localization with the SNF protein BRM in the nucleus. *Human Molecular Genetics*. 8 (4): 585-591.*

Kasten et al. 2011; SnapShot: Chromatin remodeling: SWI/SNF. *Cell* 144: 310.*

Clark; et al., "Identification of novel genes, SYT and SSX, involved in the t(X;18)(p11.2;q11.2) translocation found in human synovial sarcoma", *Nature Genetics* (Aug. 1994), 7(4):502-8.

De Leeuw; et al., "Identification of two alternative fusion genes, SYT-SSX1 and SYT-SSX2, in t(X;18)(p11.2;q11.2)-positive synovial sarcomas", *Human Molecular Genetics* (Jun. 1995), 4(6):1097-9.

Kadoch; et al., "Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy", *Nature Genetics* (Jun. 2013), 45(6):592-601.

Kadoch; et al., Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma, *Cell* (Mar. 2013), 153(1):71-85.

Roberts; et al., "Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene Snf5", *Cancer Cell* (Nov. 2002), 2(5):415-25.

Skytting; et al., "A novel fusion gene, SYT-SSX4, in synovial sarcoma", *Journal of the National Cancer Institute* (Jun. 1999), 91(11):974-5.

Svejstrup, "Synovial sarcoma mechanisms: a series of unfortunate events", *Cell* (Mar. 2013), 153(1):11-2.

Versteeg; et al., "Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer", *Nature* (Jul. 1998), 394 (6689):203-6.

* cited by examiner

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(57)

ABSTRACT

Methods and compositions are provided for treating human synovial sarcoma (SS). Also provided are screens to identify therapeutics for the treatment of synovial sarcoma. These methods, compositions, and screens are based on the discovery that promoting the assembly of wild type BAF (also called mSWI/SNF) complexes in SS cells by increasing levels of wild type SS18 and/or decreasing levels of SS18-SSX fusion protein leads to the cessation of proliferation of malignant cells in synovial sarcoma.

17 Claims, 23 Drawing Sheets
(20 of 23 Drawing Sheet(s) Filed in Color)